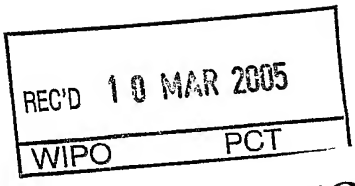
PCT/GB 2005 / 000567

INVESTOR IN PEOPLE



The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PRIORITY DOCUMENT

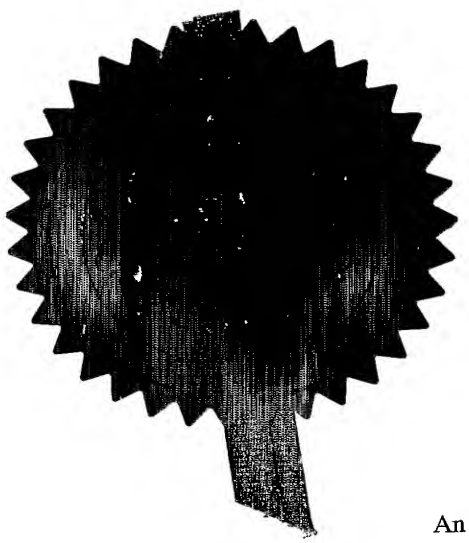
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed Stephen Hordley

Dated 11 January 2005

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
LJ
20 FEB 2004
RECEIVED BY FAX

The Patent Office

20FEB04 E874754-1 D02934
P01/7700 0.00-0403744.6 ACCOUNT ENA

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference 101358-1

2. Patent application number *(The Patent Office will fill in this part)* 0403744.6

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
SE-151 85 Södertälje
Sweden

Patents ADP number *(if you know it)* 07882448003

If the applicant is a corporate body, give the country/state of its incorporation Sweden

4. Title of the invention

CHEMICAL PROCESS

5. Name of your agent *(if you have one)* Lucy Clare PADGET

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca
Global Intellectual Property
P O Box 272
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4GR

Patents ADP number *(if you know it)* 08179707001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	10
Claim (s)	1
Abstract	
Drawing (s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 20.02.04

12. Name and daytime telephone number of person to contact in the United Kingdom — Jennifer Bennett - 01625 230148

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) For details of the fee and ways to pay please contact the Patent Office.

CHEMICAL PROCESS

The present invention relates to an improved chemical process for preparing intermediates. Certain of these intermediates are useful in the manufacture of compounds for use in the treatment of, for example, cancer, pain and cardiovascular diseases in a warm-blooded animal such as man, particularly of compounds which possess endothelin receptor antagonist activity.

In particular, the present invention relates to a chemical process for preparing [4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid which is used in the manufacture of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide which compound is disclosed as Example 36 of International Patent Application WO96/40681. That compound possesses endothelin receptor antagonist activity, and accordingly is usesful whenever such antagonist activity is desired, such as for research tools within pharmacological, diagnostic, and related studies or in the treatment of diseases and medical conditions including, but not limited to hypertension, pulmonary hypertension, cardiac or cerebral circulatory disease and renal disease. In addition this compound is also useful in the treatment of cancer and pain, in a warm-blooded animal such as man.

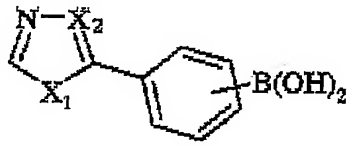
A route for preparing N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide is disclosed in International Patent Application WO 96/40681. The route involves the use of the compound N-(isobutoxycarbonylphenyl)-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide as an intermediate with the formation of the 1,3,4-oxadiazole in the 4-position of the phenyl group occurring at the end of the synthesis. This existing route is satisfactory for the synthesis of relatively small amounts of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide but is a linear rather than convergent synthesis, involving the isolation of a substantial number of intermediates. As such, the overall yield of this synthesis is not high.

Furthermore, as the heteroaryl moiety at the 4-position of the phenyl group is formed as the last step, it is necessary to undergo a linear synthesis approach with the rest of the molecule made first. This is clearly undesirable when substituents in distinct parts of the molecule need to be varied in order to investigate structure-activity relationships. It would be highly desirable if a convergent approach to the synthesis of this type of compound could be devised.

We have now devised a much improved process for the manufacture of heteroaryl-phenyl boronic acids, in particular, [4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid. The process is more convergent than the previous route and allows a reduction in the number of intermediates that must be isolated. This provides significant advantages of time and cost.

The process of the present invention utilises the increased acidity of the heteroaryl ring proton, and involves the sequential use of two bases. Initial attempts at adding one equivalent of a base to a heteroaryl-phenyl bromo compound in order to induce halogen-metal exchange led to competing deprotonation of the heteroaryl ring. On quenching with a borate ester, a negligible yield of the desired product was achieved, together with starting material and by-products. In the process of the present invention the heteroaryl ring is initially deprotonated with a (typically) "weaker" base, before inducing halogen-metal exchange with a (typically) "stronger" base.

According to a first aspect of the present invention, there is provided a process for the preparation of a compound of the Formula I



(I)

wherein,

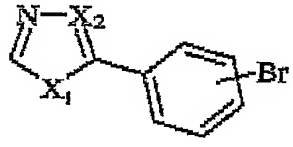
X_1 is selected from O, NR_1 or S; and

X_2 is selected from CH or N;

wherein R_1 is a nitrogen-protecting group,

which comprises ;-

the sequential reaction of a compound of the Formula II



(II)

with,

(i) methyl- or an optionally substituted aryl- lithium; and then

(ii) n-butyl-, s-butyl-, t-butyl- or n-hexyl- lithium; and then

(iii) a borate ester.

For process steps (i), (ii) and (iii), the reactions may conveniently be carried out in an inert solvent or diluent or an ethereal solvent such as diethyl ether, tetrahydrofuran,

diethoxymethane, 1,2-dimethoxyethane or 1,4-dioxan. Thus, for example, the reaction may be carried out by sequentially treating 2-(4-bromophenyl)-1,3,4-oxadiazole with 4-methylphenyllithium, followed by n-hexyllithium, and finally triisopropylborate in a suitable solvent or diluent or an ethereal solvent, for example tetrahydrofuran, at a temperature in the range, for example, -70 to -55°C, conveniently at or near -70°C.

Optionally the heteroaryl-phenyl bromo compound can be charged to a solution of the first base to enable deprotonation, followed by the addition of the second base to induce transmetallation. This method although slightly less efficient in yield and quality does have advantages in cases where the first base must be generated in situ due to lack of stability at ambient temperatures. In this case only one cryogenic vessel is required to complete the processing.

The molar ratios of the reagents used in process steps (i), (ii), and (iii), are preferably in the range from 1.0-1.5: 1.0-1.5: 2.1-3 respectively, but more preferably in the range 1.06-1.3: 1.07-1.1: 2.2-2.3 respectively. Conveniently, the lithiated intermediates formed during the conversion of a compounds of the Formula II to compounds of Formula I are not isolated as such but are each prepared and used as a solution in an organic solvent. Thereby, compounds of Formula I may be manufactured from compounds of Formula II in a one-pot procedure.

An aryl lithium is, for example, phenyl or naphthyl- lithium.

An optional substituent for an aryl lithium is, for example, methyl.

Particularly preferred optionally substituted aryl lithiums are, for example, phenyl-, 2-methylphenyl-, 4-methylphenyl-, mesityl- or naphthyl- lithium.

A borate ester is an alkyl, alkenyl or aryl boronic ester, for example, trimethyl-, triethyl- or triisopropyl- borate.

When R_1 is a nitrogen-protecting group, then, for example, suitable methods for protection are those known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991).

A suitable nitrogen- protecting group is, for example, an (1-6C)alkyl, phenyl, allyl, methoxymethyl, benzyl, triphenylmethyl or diphenylphosphinyl protecting group.

This first aspect of the present invention provides compounds of Formula I in commercially acceptable yields and of high quality.

Further values of X_1 and X_2 are as follows. Such values may be used where appropriate with any definitions, claims or embodiments defined hereinbefore or hereinafter.

X_1 is O.

X_1 is NR_1

X_1 is S.

X_2 is CH.

X_2 is N.

X_1 is O, and X_2 is CH.

X_1 is O, and X_2 is N.

X_1 and X_2 are N.

X_1 is NR_1, and X_2 is CH.

X_1 is NR_1, and X_2 is N.

X_1 is S and X_2 is CH.

X_1 is S and X_2 is N.

R_1 is allyl or benzyl.

R_1 is benzyl.

Therefore in an additional aspect of the invention there is provided a process for the preparation of compounds of the Formula I

(I)

wherein,

X_1 is selected from O, NR_1 or S; and

X_2 is selected from CH or N;

wherein R_1 is a nitrogen-protecting group;

which comprises :-

the sequential reaction of compounds of the Formula II

(II)

with,

(iv) 4-methylphenyllithium; and then

(v) n-hexyllithium; and then

(vi) triisopropylborate.

In a further aspect of the invention there is provided a process for the preparation of compounds of the Formula I

(I)

wherein,

X_1 is selected from O, NR_1 or S; and

X_2 is selected from CH or N;

wherein R_1 is a nitrogen-protecting group;which comprises :-

the sequential reaction of compounds of the Formula II

(II)

with,

(vii) methyllithium; and then

(viii) n-hexyllithium; and then

(ix) triisopropylborate.

In a further aspect of the invention there is provided a process for the preparation of compounds of the Formula I

(I)

wherein,

X_1 is O; and

X_2 is N;

which comprises :-

the sequential reaction of compounds of the Formula II

(II)

with,

(x) methyllithium; and then

(xi) n-butyllithium; and then

(xii) triisopropylborate.

In a further aspect of the invention there is provided a process for the preparation of compounds of the Formula I,

(I)

wherein,

X_1 is O; and

X_2 is N;

which comprises :-

the sequential reaction of compounds of the Formula II

(II)

with,

(xiii) 4-methyphenyllithium; and then

(xiv) n-butyllithium; and then

(xv) triisopropylborate.

Compounds of the formula **(II)** may be prepared according to the experimental methods and procedures disclosed in *Bioorganic & Medicinal Chemistry Letters*, **2002**, *12*(20), 2879-2882; *Eur. J. Med. Chem.*, **2000**, *35*, 157-162; *Helvetica Chimica Acta*, **1950**, *33*, 1271-1276; *Eur. J. Med. Chem.*, **1985**, *20*(3), 257-66 and *J. Het. Chem.*, **1989**, *26*, 1341.

The invention will now be illustrated by the following non-limiting Examples in which, unless otherwise stated:-

(i) yields are intended for the assistance of the reader only and are not necessarily the maximum attainable by diligent process development;

(ii) ^{1}H NMR spectra were determined at 270MHz in DMSOd_6 using tetramethylsilane (TMS) as an internal standard, and are expressed as chemical shifts (delta values) in parts per million relative to TMS using conventional abbreviations for designation of major peaks: s, singlet; m, multiplet; t, triplet; br, broad; d, doublet.

Example 1

[4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid

To a solution of methyllithium (8% w/w in diethoxymethane) (65 ml) was added a suspension of 2-(4-bromophenyl)-1,3,4-oxadiazole (40 g) in tetrahydrofuran (THF) (176 ml) at -65°C. A solution of n-butyllithium (2.5M in hexanes) (78 ml) was then added at -65°C. Triisopropylborate (90 ml)) was then added at -65°C. The reaction mixture was warmed to 20°C and drowned out into a mixture of acetic acid (28 ml) in water (222 ml). The resultant solid was isolated, washed with THF and water, and dried to yield the title compound (28.96 g @ 95.1% w/w, 82%); NMR Spectrum: ($DMSOd_6$) 8.00 (s, 4H), 8.31 (s, 2H), 9.35 (s, 1H); Mass Spectrum MH^+ 191.0628 (calc. using 11-B) Found 191.0633.

The 2-(4-bromophenyl)-1,3,4-oxadiazole used as a starting material was prepared as follows:

To a suspension of 4-bromobenzoic hydrazide (200 g) in industrial methylated spirit (700 ml) was added triethylorthoformate (309 ml), industrial methylated spirit (100 ml) and sulphuric acid (0.8 ml). The reaction mixture was heated to reflux for 1 hour. The reaction mixture was cooled to 0-5°C and product crystallised. Product was isolated, washed and dried to yield 2-(4-bromophenyl)-1,3,4-oxadiazole (186.1 g, 89.9%). NMR Spectrum: ($DMSOd_6$) 9.35 (s, 1H), 7.98 (d, 1H), 7.95 (d, 1H), 7.84 (d, 1H), 7.81 (d, 1H); Mass Spectrum MH^+ 224.9663 (calc. using 79-Br) Found 224.9701.

Example 2

[4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid

Lithium granules (8.2 g) and tetrahydrofuran (670 g) were charged to a reactor under an argon atmosphere and the mixture cooled to -35°C. 4-Chlorotoluene (74.3 g) was added at -35°C. The resultant solution was added to a suspension of 2-(4-bromophenyl)-1,3,4-oxadiazole (124.4 g) in tetrahydrofuran (800 g) at -65°C. A solution of n-hexyllithium (33%w/w in hexanes) (240ml) was then added at -65°C. Triisopropylborate (230.8 g) was then added at -65°C. The reaction mixture was allowed to warm to -35°C and drowned out into a solution of acetic acid (91.5 g) in water (688 g). The resultant solid was isolated, washed with THF and water, and dried to yield the title compound (92.2 g, 88%).

Example 3

[4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid

Example 2 was repeated but the charge of 4-chlorotoluene increased from 1.06 moles to 1.30 moles. The yield of the title compound increased to 89.3%.

Example 4

[4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid

Tetrahydrofuran (250 g) was charged to a mixture of lithium granules (3.02 g) and biphenyl (0.01 g) under an argon atmosphere and the mixture cooled to -30°C. 2-Chlorotoluene (27.55 g) was slowly added at -30°C. The reaction was held at -30°C for 6 hours and then cooled to -65°C. A mixture of 2-(4-bromophenyl)-1,3,4-oxadiazole (50.0 g) in THF (300 g) was slowly added at -65°C. The reaction was held at -65°C for 30 minutes then a solution of n-hexyllithium (33%w/w in hexanes, 86 ml) was added at -65°C. The reaction was held at -65°C for 30 minutes and then trimethylborate (48.7 g) was added at -65°C. The reaction was held at -65°C for 10 minutes then methanol (55.3 g) was added followed by 4-methyl-2-pentanone (240 g). The reaction mixture was warmed and the low boiling solvents distilled off under vacuum to a maximum temperature of 55°C. The residual mixture was cooled to 0°C and 10%w/w sulphuric acid (92 g) was added followed by water (92 g) whilst maintaining the temperature below 7°C. Product precipitated. The pH was adjusted to 6.5 by the addition of more 10%w/w sulphuric acid (85.3 g). The mixture was heated to 40°C then cooled back to 5-10°C. Product was isolated and washed with THF (56g) and water (60g), yielding wet title compound (25.2 g, 60%).

Example 5

[4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid

Tetrahydrofuran was charged to lithium granules (7.6 g) under an argon atmosphere and the mixture cooled to -30°C. 2-Chlorotoluene (69.4 g) was slowly added at -30°C. The reaction was held at -30°C for 6 hours then added to a suspension of 2-(4-bromophenyl)-1,3,4-oxadiazole (124.4 g) in tetrahydrofuran (800 g) at -65°C. The reaction was held at -65°C for 30 minutes then a solution of n-hexyllithium (33%w/w in hexanes, 245 ml) was added at -65°C. The reaction was held at -65°C for 30 minutes and then trimethylborate (230.8 g) was added at -65°C. The reaction was held at -65°C for 30 minutes then methanol (175 ml) was

added followed by 4-methyl-2-pentanone (600 g). The reaction mixture was warmed and the low boiling solvents distilled off under vacuum to a maximum temperature of 50°C. The reaction mixture was cooled to 5-10°C and the pH adjusted to 6.5 by the addition of 5%w/w sulphuric acid (990.5 g). Product precipitated. The mixture was heated to 40°C then cooled back to 10°C. Product was isolated, washed with THF and water, and dried yielding the title compound (79.3 g, 75.5%).

Example 6

[4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid

Example 4 was repeated but chlorobenzene (61.6 g) was used instead of 2-chlorotoluene. The isolated yield of the title compound was 87.8 g, (83.8%).

CLAIMS

1. A process for the preparation of a compound of the Formula I

(I)

wherein,

X_1 is selected from O, NR_1 or S; and

X_2 is selected from CH or N;

wherein R_1 is a nitrogen-protecting group,

which comprises :-

the sequential reaction of a compound of the Formula II

(II)

with,

(xvi) methyl- or an optionally substituted aryl- lithium; and then

(xvii) n-butyl-, s-butyl-, t-butyl- or n-hexyl- lithium; and then

(xviii) a borate ester.